IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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In re application of	:	
Edwin Mellor SOUTHERN et al.	:	Docket No. 2000-0541
Serial No. 09/559,402	:	Group Art Unit 1655
Filed April 26, 2000	:	Examiner B. Sisson
METHODS OF DETERMINING POLYNUCLEOTIDE INTRAMOLECULAR STRUCTURE (AS AMENDED)	:	

THE COMMISSIONER IS AUTHORIZED TO CHARGE ANY DEFICIENCY IN THE FEES FOR THIS PAPER TO DEPOSIT ACCOUNT NO. 23-0975

AMENDMENT

Assistant Commissioner for Patents,
Washington, D.C. 20231

Sir:

Responsive to the Official Action dated November 2, 2000, the time for filing thereto being extended for three months in accordance with the Petition for Extension submitted concurrently herewith, please amend the above-identified application as follows:

In the Specification:

Page 16, replace the paragraph beginning at line 18 with the following paragraph:

For the cooperative experiments shown in Figure 4, cold oligonucleotides corresponding to the D-loop GCTCTCCCAACT (SEQ ID NO. 1), the variable loop GACCTCCAGATT (SEQ ID NO. 2), or the TpsiC loop AACACAGGACCT (SEQ ID NO. 3), were incubated with the tRNA in the hybridisation conditions for at least 18h before being applied to the plate.

Page 20, replace the paragraph beginning at line 8 with the following paragraph:

The arrays were all hybridised under identical conditions (3.5 M tetramethylammonium chloride, 4°C) with the sequence CCTGGCACCATTAAAGAAAATATCATCTTTGGTGTTTCCTAT (SEQ ID NO. 4), part of exon 10 of the CFTR gene covered by the array.

In the Claims:

Kindly add the following claims.

--31. The method as claimed in claim 14, wherein the target is (a) a nucleic acid, (b) a protein, (c) a carbohydrate or (d) a macromolecular assembly.

32. The method as claimed in claim 31, wherein the nucleic acid is a DNA.

33. The method as claimed in claim 31, wherein the nucleic acid is a RNA.

34. The method as claimed in claim 31, wherein the macromolecular assembly is a membrane.

35. The method as claimed in claim 15, wherein the target is (a) a nucleic acid, (b) a protein, (c) a carbohydrate or (d) a macromolecular assembly.

36. The method as claimed in claim 35, wherein the nucleic acid is a DNA.

37. The method as claimed in claim 35, wherein the nucleic acid is a RNA.

38. The method as claimed in claim 35, wherein the macromolecular assembly is a membrane.

39. The method as claimed in claim 14, wherein the ligand is (a) an oligonucleotide, (b) a peptide, (c) a steroid or (d) a glycoside.

40. The method as claimed in claim 15, wherein the ligand is (a) an oligonucleotide, (b) a peptide, (c) a steroid or (d) a glycoside.

41. A method of designing a reagent to interact with a target, said method comprising studying the tertiary structure of the target according to the method of claim 14 and using the observation to design the reagent.

REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Claims 31-41 have been added. The new claims have been presented to further protect specific embodiments of the present invention. Support for the new claims is readily apparent from the teaching of the specification and the original claims. Specifically, support for the new claims can be found on page 3, lines 1-4 and 12-14, of the specification.

With regard to the Information Disclosure Statement dated April 26, 2000, a copy of which was enclosed with the Official Action dated November 2, 2000, Applicants note that the Examiner did not indicate whether the Southern et al. reference (reference "AO") has been considered. Applicants respectfully request such indication in the next Official Action.

With regard to the discrepancy contained in the transmittal sheet, Applicants believe that the transmittal sheet is correct and that the specification filed with the present application is 29 pages in length. Applicants believe that the 29 pages *include the first two cover pages of the filed PCT specification.* Applicants regrets the confusion in this regard.

With regard to the objection to the specification and the request to file a substitution specification, Applicants are confused by this requirement since the same specification from the parent application, now U.S. Patent 6,080,585, is deemed to be in proper idiomatic English. Applicants respectfully request clarification as to where, in the specification, amendments must be effected.

With regard to the objection to the specification relating to the oligonucleotide sequences disclosed therein, Applicants have amended the specification to label the oligonucleotide sequences with their respective SEQ ID Nos. (See page 16, lines 20 and 21, and page 20, line

11). Applicants believe that this amendment overcomes the Examiner's objection and places the application in compliance with 37 C.F.R. 1.821-1.825.

With regard to the objections to the claims set forth in item 6 of the Official Action, Applicants respectfully request that these objections be held in abeyance until after an indication of allowable subject matter. Applicants believe that these amendments can be more easily and efficiently effected once the allowed subject matter has been determined.

With regard to the rejection of claims 14-30 under 35 USC § 112, first paragraph, this rejection is deemed to be untenable, and is thus respectfully traversed.

The Examiner's basic argument under 35 U.S.C. §112, first paragraph, is that undue experimentation would be required in order to practice the claimed invention with a ligand or target which are not nucleic acid.

However, Applicants believe that the experimentation would not be undue since the invention is not complex or difficult in practice. It uses immobilised arrayed ligands to "probe" the tertiary structure of a target molecule and identify the regions of the target molecule which are free to interact with ligands.

The present invention also offers ways of identifying "co-operative" ligands i.e. two ligands which, when combined, can each bind to the target but which, when separate, might not. Typically, a target will be incubated with a compound library or with an array of potential ligands and a first ligand will be identified. That ligand will then be bound to the target (in solution, not on the array) and the target-ligand complex will be incubated with the array. If the target-ligand complex binds to ligands which the target alone did not, it is inferred that binding of the first

ligand reveals a "cryptic" binding site in the target for the second ligand. The second ligand would never be identified by a normal screening method.

These two aspects of the present invention are disclosed in claims 14 and 15, respectively.

The invention in practice operates very straightforwardly. All one skilled in the art needs is (i) a target, (ii) an array of a potential ligands, and (iii) a way of detecting if the target has interacted with a ligand in the array, for example, by labelling the target. Once a skilled artisan has these three things, putting the invention into practice requires no undue experimentation.

The priority date of the present application is in early 1994. As mentioned in the response filed for the parent application in January 1998, nucleic acid arrays and peptide arrays were both known and available at that time. Relevant documents include WO93/09668 and WO94/05394.

For example, nucleic acid arrays and protein targets were known at the priority date. All that is required for one skilled in the art to practice the claimed invention for this ligand-target pair (claim 14 or claim 15) is to label the protein such that the locations of any interactions with the immobilised ligands can be observed. Thus, it is clear that the present invention is enabled since this experiment would not have required any undue experimentation. The Examiner's assertion that the claimed invention would require "immense" experimentation is clearly wrong. In fact, the above experiment would only differ from the Examples disclosed in the specification in that the interaction between target and ligand results not from nucleic acid/nucleic acid hybridization but from protein/nucleic acid interactions. As proteins and nucleic acids were known to interact in 1994, including aptamer-protein interactions, and the molecular basis for

this interaction had been studied in detail, it would have been routine to adapt the Examples of the specification (nucleic acid target/nucleic acid ligand) to use a protein target instead. As mentioned on page 3, lines 9-12, of the specification, "the nature of the interaction is not material to the invention".

Similarly, peptide arrays were known at the priority date, as were protein targets. To practice the claimed invention with this ligand-target pair (claim 15), All that is required for one skilled in the art is to label the protein target. Again, such an experiment would have been enabled since it would not have required undue experimentation to practice the claimed method using this type of target and prior art peptide. Indeed, by 1995, there were publications describing this type of experiment (e.g. Holmes et al. (1995) The use of light-directed combinatorial peptide synthesis in epitope mapping. Biopolymers 37:199-211).

Like the nucleic acid arrays and protein targets above, the effort involved in doing these experiments would have been routine and not undue and be comparable to the effort involved in repeating the Examples of the specification. The only real difference between the Examples of the specification and the present experiments is the molecular interactions which underpin the target/ligand binding (again, see page 3, lines 9-12), but experimental procedure and effort are similar and thus routine.

As a result, since the enablement of the presently claimed method has been acknowledged by the Examiner for nucleic acid targets and ligands, the enablement for other targets and ligands should also be recognised and acknowledged by the Examiner.

The Examiner has objected to the supposed lack of disclosure of "reaction conditions, or a range of reaction conditions under which a variety of analyte ligand interactions can be evaluated". However, such an argument ignores, for example, that protein/nucleic acid and protein/protein interactions were well known and had been widely studied (in other experimental contexts) as of the priority date. One skilled in the art was already in possession of such relevant information (temperatures, concentrations, pH etc.). The Examiner seems to be suggesting that, faced with ligands in an array rather than free in solution, a skilled artisan would have to re-confirm that proteins are denatured at high temperatures and extremes of pH, for instance. However, Applicants argue that a skilled artisan would not have to "re-invent the wheel" when practicing the claimed invention. The "rules" of chemistry still apply on an array just as it would in solution.

Applicants also wish to note that under U.S . practice, the test of enablement is whether one skilled in the art could practice the claimed invention from the disclosures in the specification ***coupled with information already known in the art*** without undue experimentation. *United States v. Telectronics, Inc., 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); In re Stephens, 529 F.2d 1343, 188 USPQ 659(CCPA 1976).* A specification ***need not teach***, and preferably omits, ***what is well known in the art***. *Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 3 USPQ2d 1737 (Fed. Cir. 1987).* Thus, since, as shown above, the interactions of other target/ligands such as protein/nucleic acid and protein/protein are well known to and well studied by one skilled in the art, such disclosures of temperatures,

concentrations, pH etc. need not be taught or reiterated by the specification as allowed under U.S. practice.

Therefore, the Examiner's assertion that practicing the present invention using targets and/or ligands which are not nucleic acids require undue experimentation, is clearly wrong. In addition, the view that the experiments described above would require "immense" experimentation and "many man-years of labor" is also clearly incorrect.

In further support of the Applicants' arguments, Applicants have submitted an article for the Examiner's review and consideration. Recently, arrays of small molecules have been described (see e.g. MacBeath et al. (1999) JACS 121:7967-7968) for studying protein-ligand interactions in parallel. The arrays were prepared in a manner analogous to the section on pages 14 and 15 of the specification entitled "Making arrays." A glass plate was derivatised with a linker, and ligands were then applied to the plate in the form of an array. There is no evidence that the work of MacBeath et al. took "many man-years" or that it required "immense" or undue experimentation or that the authors experienced insurmountable difficulties in preparing and using the arrays.

Thus, since the representative Examples of nucleic acid arrays with nucleic acid targets have been shown in the specification to be enabling, one skilled in the art would also have been able to practice different ligands on the array and/or different targets in the same way as taught in the claims based on the teachings of the specification ***and the knowledge well known to one skilled in the art***. In other words, it would have only require routine experimentation to identify the regions of the target that are open to interaction with ligands etc. as set out on page 23 of the

specifiation. As a result, Applicants submit that the rejection of claims 14-30 under 35 USC § 112, first paragraph, cannot be sustained in view of the arguments above and should be withdrawn.

With regard to the rejection of claims 14-30 under the judicially created doctrine of obviousness-type double patenting over claims 1-13 of USP 6,080,585, this rejection has been overcome by the filing of a Terminal Disclaimer submitted herewith.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

In view of the foregoing amendments and remarks, it is respectfully submitted that the Application is now in condition for allowance. Such action is thus respectfully solicited.

If, however, the Examiner has any suggestions for expediting allowance of the application or believes that direct communication with Applicants' attorney will advance the prosecution of this case, the Examiner is invited to contact the undersigned at the telephone number below.

Respectfully submitted,

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